General Capstone cover sheet

Name: Praise Ogwuche

Project title: "Advancing Male Contraception:
Part 1 - Literature Review of YCT-529 and Male Contraceptive Methods;
Part 2 - In Silico Evaluation of YCT-529's Pharmacokinetics and Clinical Potential"

Abstract:

PART 1

YCT-529, chemically known as 4-[5-[2,2-dimethyl-4-(4-methylphenyl)chromen-6-yl]-1H-pyrrol-2-yl]benzoic acid, is a highly selective non-hormonal oral male contraceptive that competitively binds retinoic acid receptor alpha (RARα), displacing endogenous retinoic acid (RA) and locking the receptor in an inactive conformation. This inhibits coactivator recruitment and suppresses transcription of RA-responsive genes essential for spermatogenesis. Its chromene core, pyrrole linker, and benzoic acid group confer RARα selectivity while minimizing RARβ/γ cross-reactivity. Preclinical murine studies showed a 99% reduction in sperm count with full reversibility in 4 weeks, no hormonal disruption, and maintained libido. Mouse pharmacokinetics revealed an 11-hour half-life, 2.1 μM peak plasma level, and significant testicular accumulation. In non-human primates, oral dosing at 10–20 mg/kg/day achieved full sperm suppression without systemic toxicity.

PART 2

This study applies physiologically based pharmacokinetic (PBPK) modeling to characterize YCT-529's pharmacokinetics across diverse populations and dosing conditions. Using PK-Sim and ADMETLab 3.0, I simulated 16,000 virtual participants (4,000 per group: Black Americans, East Asians, White Americans, Europeans) across four doses (15, 45, 90, 180 mg). Atazanavir served as a validation reference, confirming model reliability. YCT-529 exhibited rapid absorption (Tmax = 1–3 h) and dose-dependent systemic exposure (Cmax: ~50 μg/L at 15 mg to ~500 μg/L at 180 mg). East Asians showed the highest plasma retention, while Black Americans had the lowest—consistent with known CYP3A4 metabolic variability—suggesting that race-specific dosing regimens be considered in early-phase trials. Dietary state significantly influenced absorption: fasting raised mean Cmax to 45.85 μg/L versus 30.58 μg/L (light meal) and 28.32 μg/L (high-fat), with large effect sizes ($d = 1.38–1.61$, $p < 0.001$). However, convergence at ~40 μg/L after 10 hours suggests steady-state exposure is diet-independent. These findings recommend consideration of both dietary conditions and ethnicity in Phase I dosing strategies.

I have read/completed the following and reached out about any questions:

PO I have read the Capstone Handbook.
PO I have read the most current version of the HC changes at the bottom of this page.

PO I have updated my Capstone information in this sheet using this form. *PO* I understand the systems/processes that my group will be using.	
Links to working files	
Main folder(s)	https://drive.google.com/drive/folders/1HYKwnz8wegf2E_r_vVCPa0dK9bep7Jwn?usp=sharing
Paper/writeup *(e.g., Google Doc, Overleaf)*	Overleaf: https://www.overleaf.com/read/tdwrjxjkmttc#8fea41 Google Drive: https://drive.google.com/file/d/1Fnj3CPzHsQolslvTLY0x2Iw8xbd7EBTI/view?usp=sharing
Slides, images	Full drive: https://drive.google.com/drive/folders/1HYKwnz8wegf2E_r_vVCPa0dK9bep7Jwn?usp=sharing
Data and analysis	https://drive.google.com/drive/folders/1aNzhYjV4fwAKMfu8Sjh9Xx_S3eiyMBtl?usp=sharing
GitHub	https://github.com/PraiseOgwuche/YCT-529_PBPK_Modeling
My HC & LO plans, applications, annotations [template]	https://drive.google.com/file/d/1zaV3INUExafPP0bZoX3gM4Wx7VATQP3A/view?usp=sharing https://drive.google.com/file/d/1jZJCmh6S_sq8DL7gt4kFFNY6Dr7AWwGu/view?usp=sharing CAPSTONE LOs **#cp-curation:** I carefully curated my capstone submission to ensure clarity, accessibility, and completeness. This included organizing key components such as the cover sheet, executive summary, main capstone work products, and the HC and LO Appendices. Each section was formatted to meet academic standards while maintaining coherence for diverse audiences. By structuring my work logically and integrating relevant visuals (e.g., graphical abstracts, methodology flowcharts, and pharmacokinetic plots), I enhanced the clarity and accessibility of my research. My submission not only met but surpassed the required quality standards by ensuring a well-curated and streamlined presentation. **#cp-navigation:** In managing my capstone project, I employed a focused and adaptive approach to ensure steady progress while meeting key deadlines. My strategy included:

- Hosting weekly Friday meetings with my team to review progress, refine goals, and troubleshoot challenges.
- Adjusting project scope dynamically, leading to the integration of molecular modeling and social science analysis in the evaluation of YCT-529 based on iterative feedback.
- Prioritizing structured planning over rigid scheduling, moving away from my initial Gantt Chart approach to a more flexible system that allowed me to adapt to emerging insights without compromising deadlines.

By strategically balancing structure and adaptability, I ensured the successful completion of my project while effectively managing evolving research directions.

#cp-outcomeanalysis: To accurately assess the viability of YCT-529, I implemented targeted metrics and evaluation criteria tailored to the scope of my project. This included:

- Comparing YCT-529's preclinical performance against established contraceptives, evaluating efficacy, safety, and reversibility as key benchmarks.
- Using structured rubrics to assess how well my literature review synthesized existing research, ensuring the project met rigorous academic standards.
- Critically analyzing my research findings to determine whether the study successfully addressed its objectives and contributed meaningful insights into contraceptive development.

For my pharmacokinetics research, I ensured a comprehensive and validated modeling approach by:

- Developing a detailed PBPK model for YCT-529, structured to reflect real-world ADME properties.
- Validating my model using Atazanavir and a placebo, confirming the accuracy of my pharmacokinetic predictions.
- Writing evidence-based discussions that linked my

	observations to known drug metabolism mechanisms, ensuring scientific rigor and clinical relevance. By integrating these structured evaluation methods, I maintained high research quality, analytical depth, and methodological integrity, ensuring that my work was both robust and impactful in the field of male contraceptive development. **#cp-qualitydeliverables:** Submit work products with the scope, depth, and rigor appropriate to the setting or stage of the project. I have submitted a comprehensive two-part capstone project that demonstrates depth, interdisciplinary application, and analytical rigor. Across these two parts, I applied 8 LOs spanning my two majors and integrated insights from at least 18 HCs. My work meets and exceeds expectations by: ● Producing rigorous scientific analysis in both my literature review and pharmacokinetic modeling, ensuring a well-substantiated and methodologically sound investigation. ● Ensuring clarity and accessibility by supplementing my technical research with two Medium articles, distilling complex findings for a broader audience. ● Adhering to high academic standards, demonstrating mastery of scientific communication, computational modeling, and critical evaluation. By thoughtfully balancing depth of research, interdisciplinary integration, and accessibility, my capstone delivers a high-quality, well-rounded, and impactful final product.
Planning & progress tracking workspace (Notion, etc.)	I was initially using Notion and time management software but then I resorted to late nights and leveraging holidays to do my work.
Other *(please specify and add,*	Nil

edit, or delete rows according to your project) *[Tools and systems for project management]*	
Since the last assignment was submitted	

Summary of all changes and progress (Your advisor may suggest that you highlight changes from the previous assignment in a different font color)	• On Research:
	  ○ I addressed feedback from the revised full draft
	  ○ I adjusted the figures
	  ○ Included information about my validation of python-generated outputs with PK-Sim outputs
	  ○ Added more information about SMILES, PK-SIM and ADMETLab3.0 in the main paper
	  ○ Did a complete significance test on the dietary conditions
	  ○ Added my name to both papers
	  ○ Improved the limitation section by adding a discussion on the sociological barriers to widespread acceptance of this revolutionary medicine
	• On Literature
	  ○ Refined the HC and LO applications
	  ○ Adjusted boxes around figures

Brief reflection on my progress and process so far	• Thank you for getting me through this Capstone!
Feedback implemented	• This has been discussed in the Changes I made so far
For this submission	
Request for feedback on these specific areas	• Nil
If you are doing an interdisciplinary minor...	
What is your interdisciplinary minor?	Nil
Have you read the Capstone requirements for your	☐ Yes ☐ No

interdisciplinary minor?	
Do you plan to propose your capstone as qualifying for this minor?	☐ Yes ☐ No
If your answer to the question above is "Yes", in what ways do you think this capstone is relevant to your interdisciplinary minor? Please specify!	Nil
AI Statement	
A statement on AI use is required for all assignments (Failure to include a sufficiently explained AI statement will result in grade penalties)	**Use of AI in Writing and Editing** In the writing and completion of my papers, I carefully considered the role of AI tools in assisting with efficiency while ensuring the integrity of my writing remained uncompromised. Initially, I drafted paragraphs in Google Docs and used ChatGPT to refine the language, correct grammatical errors, and enhance professionalism. However, my advisor pointed out that some of my sentences appeared vague and lacked depth—likely due to how I used AI. The AI's limited contextual understanding of my subject matter often resulted in generalized or incoherent revisions, which diminished the precision and clarity of my intended message. Recognizing this, I refined my workflow to maintain greater control over my writing, ensuring that AI serves only as a supplementary tool rather than a primary editor. For these papers—the literature review and the research paper—I did not use ChatGPT for drafting or editing any part of the main content. Instead, I used Writefull, an AI-powered grammar assistant available on Overleaf. Writefull highlights grammatical errors without altering sentence structure or meaning and offers two language model options: its own academic writing model and a GPT-based model for general texts. I exclusively used Writefull's academic model to ensure my writing was polished while retaining my intended meaning. I manually reviewed each suggested grammatical correction to ensure only relevant changes were made, preserving the clarity and specificity of my arguments. You can explore Writefull at:

https://www.writefull.com/writefull-for-overleaf.

Use of AI in LaTeX Code Generation

I used ChatGPT for help with LaTeX code. Writing academic papers in LaTeX is time-consuming, and while I am proficient with LaTeX, I occasionally used AI to improve efficiency in formatting.

For example, when inserting figures, I used a standard LaTeX template for figure placement. To save time, I asked ChatGPT to generate concise figure captions based on my image descriptions. I then reviewed and edited each caption to ensure scientific accuracy.

I also frequently use the Vancouver citation style in my references. When I had citations formatted in APA style from journal sources or early drafts, I used ChatGPT to convert them into Vancouver style. I manually verified each AI-generated citation against the original reference to ensure accuracy before including it in my bibliography.

In addition, I used ChatGPT to clarify LaTeX commands such as modifying table formatting, aligning equations, and fine-tuning bibliography settings when I needed help with specific syntax or implementations.

How I Use AI in Academic Writing - Generally

Through experience, I've learned that AI works best as a supplementary tool—not as a replacement—for academic writing and critical thinking. AI tools are useful for grammar checks, generating LaTeX code, and handling citation formatting, but they do not replace human judgment, especially when conveying complex ideas that require depth and precision.

I intentionally avoided using AI for content editing beyond grammar checking to ensure that my arguments, terminology, and application of concepts stayed true to the academic rigor expected in this field. AI does not understand LOs or how I applied specific knowledge from class, so relying on it for major edits weakens the accuracy of my work..